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REVIEW

The Development of mRNA Vaccines for Infectious Diseases: Recent Updates

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Abstract: mRNA-based technologies have been of interest for the past few years to be used for therapeutics. Several mRNA vaccines for various diseases have been in preclinical and clinical stages. With the outbreak of the COVID-19 pandemic, the emergence of mRNA vaccines has transformed modern science. Recently, two major mRNA vaccines have been developed and approved by global health authorities for administration on the general population for protection against SARS-CoV-2. They have been proven to be successful in conferring protection against the ongoing SARS-CoV-2 and its emerging variants. This will draw attention to various mRNA vaccines against infectious diseases that are in the early stages of clinical trials. mRNA vaccines offer several advantages ranging from rapid design, generation, manufacturing, and administration and have strong potential to be used against various diseases in the future. Here, we summarize the mRNA-based vaccines in development against various infectious diseases.

Keywords: vaccines, mRNA, infectious diseases, lipid nanoparticles, immune response

Introduction

Vaccines are important for protection against infectious agents and confer protection against various diseases to humans[1]. Vaccines have been prominent in eradicating various deadly diseases such as smallpox, polio, measles, mumps, rubella, and other such infections.[2–4] Conventionally, vaccines were developed using chemical or heat treatment and live attenuated pathogens in cell lines or animals. While live attenuated vaccines (LAV) have been successful in the eradication of numerous deadly diseases, their safety and efficacy remain questionable in some diseases.[2] Some disadvantages of live attenuated vaccines include their failure if there are mutations in the surface antigens of the pathogens, causing the disease in immune-compromised individuals and chances of reversion to a virulent form due to reverse mutations in the pathogen.[5,6] These vaccines are less efficient in mounting $CD8^+$ immune response, which is important for protection against bacteria and viruses.[7]

Recently, nucleic acid therapeutics have emerged as an alternative to conventional vaccines. One of the nucleic acid vaccine approaches involves the development of messenger ribonucleic acid (mRNA) vaccines.[8] The first mRNA vaccine was developed in rats to reverse diabetes insipidus using intrahypothalamic injection of vasopressin mRNA.[9] mRNA vaccines are thought to be beneficial in comparison to the conventional vaccines due to the non-infectious and non-integrative nature of mRNA in the human body.[10] Additionally, mRNA half-life can be modulated in a cell by adding modifications onto the mRNA molecule.[10]

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Nucleic acid-based vaccines mimic infection with live pathogens and stimulate follicular T helper and germinal B cell immune response.[11]

Here we review different types of mRNA vaccines, delivery, and immune responses generated by mRNA vaccines and various mRNA-based vaccines against infectious diseases in clinical trials.

Types of mRNA Vaccines

Currently, there are two forms of mRNA vaccines: non replicating mRNA vaccines (modified and unmodified mRNA (NRM)) and self-amplifying mRNA (SAM) vaccines, which are derived from positive-strand RNA virus.[12–17] mRNA vaccines are produced by artificially synthesizing mRNA via a cell-free in vitro enzymatic transcription reaction. This in vitro reaction consists of linearized plasmid DNA, RNA polymerase and nucleoside triphosphates. NRM vaccines consist of an open reading frame (ORF) for a target antigen, untranslated regions (UTRs) at both ends and a terminal poly A tail.[18] Once inside the body, they drive antigen expression. Naked unmodified mRNA is prone to be degraded as soon as it is delivered inside the body. However, it was discovered that incorporation of naturally occurring chemically modified nucleosides such as pseudouridine and 1-methylpseusouridine results in the efficient translation of RNA.[19,20]

Another mRNA vaccine platform is based on alphavirus, a positive-strand virus.[21] In these vaccines, the structural proteins are replaced with the gene of interest. These self-amplifying mRNA can direct self-replication RNA-dependent RNA polymerase complex and generate multiple copies of the antigen-encoding mRNA.[22] They express high levels of the heterologous gene when introduced into the cytoplasm of host cells. They mimic the production of antigens in vivo by viral pathogens and trigger both humoral and cellular immune responses.[22] SAMs produce higher levels of antigens as compared to NRM vaccines. Both NRM and SAM vaccines do not integrate into the host genome. mRNA vaccines are much safer than other vaccine platforms and hold promise to be effective against infectious pathogens.[13,15,20,23,24]

Delivery of mRNA Vaccines

The delivery of mRNA vaccines is crucial due to their unstable nature. Intravenous administration of unmodified mRNA leads to its digestion by ribonucleases and stimulates innate immune response.[25,26] The immune system cells including antigen-presenting cells (APCs), B cells and T cells should be stimulated by mRNA delivery.[27–29] Delivery of mRNA molecules is challenging as mRNA molecule is 4 times larger than other molecules. In addition, mRNA is negatively charged and repulsed by the cell membrane.[30] This limitation can be overcome by using modified RNA and better delivery systems. Various mRNA platforms have been designed including protamine, dendrimers, polyethyleneimine and lipid nanoparticles.[31] Lipid nanoparticles (LNP) loaded with nucleoside modified NRM is used often for administering these vaccines generally in clinical trials.[31] LNPs are composed of phospholipids, cholesterol, ionizable lipids and lipid-anchored polyethylene glycol (PEG).[32] LNPs help cellular uptake, aid endosomal uptake, and enhance cytoplasmic delivery.[33] LNPs also protect mRNA from being recognized by endosomes and toll-like receptors (TLRs) and prevent overactivation of the innate immune system.[34] Some mRNA vaccines have adjuvant properties, which can be beneficial.[35] mRNAs can be modified to enhance immune activation without blocking mRNA expression. This includes modification of a nucleoside with a TLR-4 agonist monophosphoryl lipid A (MPLA) which aids in the induction of T cell activation.[36,37] Another strategy employed is using a short double-stranded region in poly-A tail or 3′UTR of mRNA. The addition of a short poly U or poly-A tail induces IFN-B and IL-6 and enhances dendritic cell activation and migration. The ds poly U or poly-A tail is recognized by TLR3 and RIG-I.[10,38] Recently, two SARS-CoV-2 RNA lipid nanoparticle vaccines based on nucleoside modified mRNA (modRNA) were designed.[39,40] BNT162b1 is a modRNA with blunted immune sensor activating capacity and enhanced RBD expression.[41] BNT162b2 is a modRNA vaccine that expresses P2 mutant, prefusion spike glycoprotein (P2 S) (version 9).[42,43]

Immune Response to mRNA Vaccines

The mechanism of immune response to mRNA vaccine is still being studied. In humans, there are two kinds of RNA sensors the RIG-I-like receptor family and TLRs.[38] There are four TLRs: TLR3, TLR7, TLR8 and TLR9 which are present in dendritic cells, macrophages, and monocytes. TLR3 recognizes double-stranded RNA (dsRNA) and single-stranded RNA (ssRNA). TLR7 binds to both dsRNA and ssRNA and TLR8 recognizes ssRNA only.[44,45] The RIG-I family includes RIG-I, MDA-5 and LGP2. RIG-I

recognizes ssRNA and dsRNA and stimulates interferon production.[46,47] MDA5 is a cytosolic RNA sensor that detects long ds RNA generated during viral RNA replication. This recognition of ds RNA activates IRF-3 and NF-KB and increased the production of IFN-I.[48,49] The induction of interferons (IFNs) by mRNA vaccines depends on the in vitro transcribed mRNA, administration route and the delivery vehicle.[50] Post-mRNA vaccination, pattern recognition receptors (PRRs) are activated, and there is enhanced type I IFN production.[51] The IFN production can be positive via activation of the immune response or negative by blocking mRNA translation.[52]

Vaccine-Induced Immunity

A cellular immune response such as cytotoxic T cells (CTLs) directly targets the viral-infected cells in contrast to neutralizing the virus, which is achieved by humoral immunity.[53,54] The level of antibody generation depends on the size of LNPs which are transport to the draining lymph nodes, thus activating B cells. B cells can uptake the LNPs with mRNA and facilitate the production of protein from the mRNA.[55] In addition, B cells interact with the B cell receptors expressing the foreign antigens. B cells located in the draining lymph nodes (with the LNP-mRNA) secrete specific low-affinity antibodies and some may enter a germinal center (GC).[56] B cells that enter GC undergo somatic hypermutation (SHM) and affinity maturation. The affinity matured B cells later become plasmablasts and secrete high-affinity antibodies. However, they can also re-enter GCs that undergo SHM and become memory B cells[57] (Figure 1).

For efficient CTL induction, antigen should enter the route of antigen processing. The pathogenic antigens are then delivered to the cytosol for proteasomal processing. Later, the peptides generated from the proteasomal pathway are delivered to the endoplasmic reticulum (ER) by the transporter associated with antigen processing (TAP).[58] In the ER, these peptides bind to the major histocompatibility complex class I (MHC). The MHC I-antigen peptide complex is then recognized by the CD8 T lymphocytes at the cell surface.[59] mRNA-based vaccines are particularly suitable for the generation of potent CTL responses because they can express the antigen in the cytosol of the antigen-presenting cells.[60,61]

Antigen Selection

While designing mRNA-based vaccines, various factors such as antigen selection, vaccine platforms, vaccine routes and regimen must be taken into consideration. Antigen selection is a crucial step for vaccine design.[62] In the case of SARS-CoV-2, the structural proteins are S protein, N protein, matrix protein (M) and envelope protein (E). N protein is responsible for coating the large positive-strand RNA genome encased in a lipid envelope derived from the host cell membrane. S, M and E proteins are inserted into this membrane.[63] It has been found that in SARS-CoV-2 only the antibodies against the S protein can neutralize the virus and prevent infection. Therefore, most of the vaccines for SARS-CoV-2 are directed against the S1 domain of the receptor-binding domain.[64]

RNA Vaccines in Infectious Diseases

SARS-CoV-2

COVID-19 is caused by SARS-CoV-2 (severe acute respiratory syndrome–coronavirus 2) that causes respiratory illness, which in severe cases can lead to death.[65] Bats are the main host of coronavirus and when transmitted to humans[66]; it is primarily spread via direct transmission. Coronavirus is composed of spike protein (S), envelope protein (E), membrane protein (M), nucleocapsid protein (N) and hemagglutinin esterase dimer protein (H) which are bound to negative sense RNA.[67] COVID-19 is an infectious disease and emerged as a global pandemic in December 2019. Therefore, there is an urgent need to develop a vaccine against the SARS-CoV-2 virus. Various COVID-19 vaccines have been in development since the beginning of the pandemic.[68] BNT162b2 is a lipid nanoparticle-formulated nucleoside-modified RNA vaccine. It encodes a prefusion stabilized, membrane-anchored SARS-CoV-2 full-length spike protein. This vaccine was approved by the FDA in December for administration on the public after it showed 95% efficacy in Phase 3 clinical trials.[69,70] A few weeks later, mRNA1273, which is also a lipid nanoparticle-encapsulated mRNA-based vaccine encoding the prefusion stabilized full-length spike, was approved by the FDA after its efficacy was 94.1% in phase 3 clinical trials (Table 1).[71,72] Currently, CV2nCoV containing sequence-optimized unmodified mRNA coding for a stabilized form of spike protein encapsulated in lipid nanoparticles (LNP) remains in preclinical development. CV2nCoV elicits high titers of cross-neutralizing antibodies against the B.1.1.7, B.1.1.298 and B.1.351 variants in rat.[73] CV2nCoV is optimized to have enhanced translation, immunogenicity, and 1.8-fold higher protein expression than the previous candidate vaccine CVnCoV.[73,74] CVnCoV showed 47%

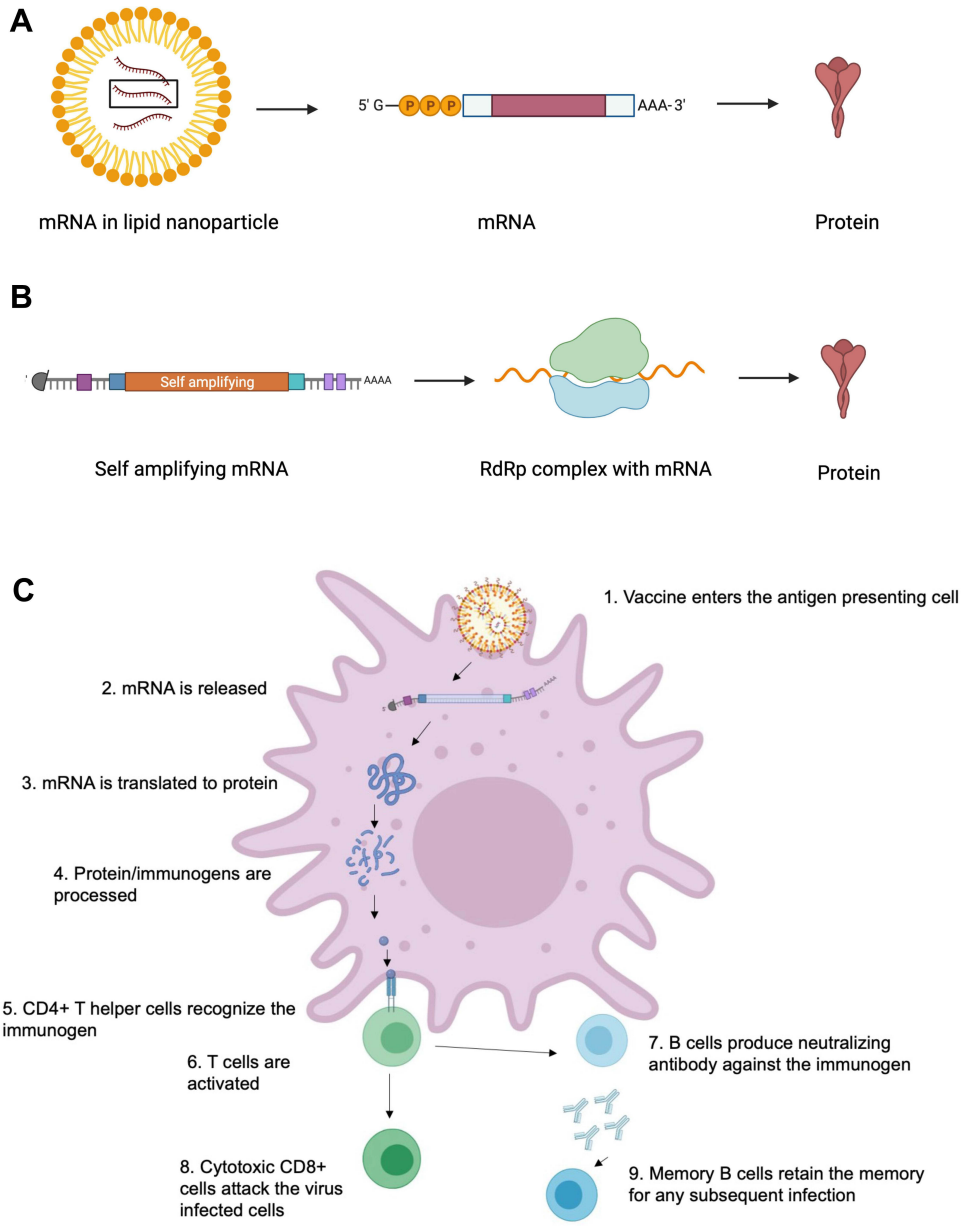


Figure 1 The mechanisms of mRNA vaccine. (**A**) mRNA vaccine in lipid nanoparticle when released in the body is translated to protein which then elicits immune response. (**B**) Self amplifying mRNA is released into the body and then complexed with RdRp which is then translated into protein and elicits immune response. (**C**) mRNA vaccine elicits immune response as the protein is expressed and recognized by CD4+ T helper cells; this activates CD8+ T and B cells. B cells produce neutralizing antibodies and memory B cells retain the memory for any subsequent infection. CD8+ T cells attack virus-infected cells. Created with BioRender.com.

efficacy against SARS-CoV-2 of any severity in Phase II/III clinical trials and failed to meet prespecified statistical success criteria[75] (NCT04652102). It has been now withdrawn from the regulatory review due to a potential overlap with approval timelines for CV2nCoV (CureVac).

ARCoV is another such lipid nanoparticle-encapsulated mRNA (mRNA-LNP) encoding the receptor-binding domain (RBD) of SARS-CoV-2 is in Phase III clinical trials (NCT04847102). ARCoV elicited high SARS-CoV-2 specific IgG antibodies and strong virus neutralization titers in mice and cynomolgus monkeys.[76]

mRNA vaccines can be generally designed faster than any other platform. This is evident from the SARS-CoV-2 nucleoside modified mRNA-LNP vaccine for human use in 42 days post obtaining the SARS-CoV-2 sequence by Pfizer-BioNTech and Moderna.[77,78] mRNA-based vaccines may prove to be better than other platforms and efficacious against the mutant virus strains as the mRNA can be designed for a mix of multiple sequences for a broad coverage during

Table 1 mRNA Vaccines Against Infectious Diseases

Disease	Vaccine/Funding Source	Dose Regimen	Phase	Outcome/Efficacy	Platform	References
SARS-CoV-2	BNT162b2, Pfizer-BioNTech	Two-dose regimen, 21 days apart, delivered in the deltoid muscle	Approved	95% (95% CI, 90.3 to 97.6)	LNP- encapsulated full-length spike mRNA	[69]
SARS-CoV-2	mRNA-1273, Moderna	Two-dose regimen, 21 days apart, delivered in the deltoid muscle	Approved	94.1% (95% CI, 89.3 to 96.8%)	LNP- encapsulated full-length spike mRNA	[88]
SARS-CoV-2	CV2nCoV/CVnCoV, CureVac AG	Two-dose regimen, 21 days apart, delivered intramuscularly	Preclinical	N/A	LNP- encapsulated sequence optimized spike mRNA	[140]
SARS-CoV-2	ARCoV, Walvax Biotechnology, PLA	Two-dose regimen, 28 days apart, delivered intramuscularly	Phase III	N/A	LNP- encapsulated full-length RBD mRNA	NCT04847102
Rabies	CV7201, CureVac AG	Three-dose regimen, delivered intradermally or intramuscularly	Phase I	GMT of 0·73 IU/mL (95% CI 0·36–1·46)	LNP- encapsulated full-length RABV-G mRNA	[96]
Rabies	CV7202, CureVac AG	Three-dose regimen, delivered intramuscularly	Phase I	GMTs of 4186 U/mL (13,253–88,185) and 20,707 U/mL (5592–76,678) for 1 and 2 μg groups	LNP- encapsulated full-length RABV-G mRNA	NCT03713086 [95]
Influenza	mRNA-H10N8, mRNA-H7N9, Moderna	Two-dose regimen, delivered intramuscularly	Phase I	For H10N8 HAI GMT was 13.9, for H7N9 HAI GMT was 13.6	LNP- encapsulated full-length HA glycoprotein mRNA from the H10N8 and H7N9 strain	[104]
Respiratory syncytial virus (RSV)	mRNA-1345, Moderna	Three-dose regimen, delivered intramuscularly	Phase I	GMF of 20.5 for RSV-A and GMF of 11.7 for RSV-B for young adults, GMF of 14.2 for RSV-A and GMF of 10.1 for RSV-B for older adults	LNP- encapsulated prefusion F protein	ModernaTx NCT04528719
Human metapneumovirus (HMPV) and parainfluenza virus type 3 (PIV3)	mRNA-1653, Moderna	Three dose regimen, delivered intramuscularly	Phase Ib	GMT of 6.04 for HMPV-A, 6.33 for HMPV-B and 3.24 for PIV3	LNP- encapsulated F protein coding mRNA from hMPV and PIV3	ModernaTx NCT04144348 NCT03392389

(*Continued*)

Table 1 (Continued).

Disease	Vaccine/Funding Source	Dose Regimen	Phase	Outcome/Efficacy	Platform	References
Human cytomegalovirus (HCMV)	mRNA-1647, Moderna	Three-dose regimen, delivered intramuscularly	Phase III	GMRs of 13.4–40.8	LNP- encapsulated six mRNAs coding the HCMV pentamer complex and gB antigens (UL128, UL 130, UL131, gB, gH, gL)	ModernaTx NCT05085366
Zika virus	mRNA-1893, Moderna	Two-dose regimen, delivered intramuscularly	Phase II	GMT of 1415 post dose two	LNP- encapsulated prME structural protein coding mRNA	ModernaTx NCT04917861
Epstein–Barr virus (EBV)	mRNA-1189, mRNA-1195 Moderna	N/A	Preclinical	10^3 and 10^5, B-cell and epithelial neutralization titers in mice	LNP- encapsulated four mRNAs coding the EBV glycoproteins (gp42, gp220, gH, gL)	ModernaTx
Human immunodeficiency virus (HIV)	HIV SAM, Env/MF59 and HIV-VRP vaccines, Biomedical Primate Research Centre, Rijswijk, The Netherlands	Three-dose regimen, delivered intramuscularly	Preclinical	GMTs of $10^{6.14}$, $10^{6.25}$, and $10^{4.79}$ for Env/MF59, HIV SAM, and HIV-VRP respectively in rhesus macaques	Cationic nanoemulsion encoding HIV-1 TV1 Env gp140, HIV-1 TV1 Env gp140, HIV-1 TV1 Env gp140 protein with MF59	[24]
Human immunodeficiency virus (HIV)	HIV-1 antigen Gag vaccine, Virology Unit, Institute of Tropical Medicine, Antwerp, Belgium	Subcutaneous immunization of Balb/c mice	Preclinical	Secretion of type I interferon (IFN) and the recruitment of monocytes to the draining lymph nodes	HIV-1 antigen Gag complexed with the cationic lipid DOTAP/ DOPE	[50]
Streptococcus	SAM vaccine, GlaxoSmithKline	Intramuscular immunization of CD-1 mice	Preclinical	GMT ratio of 10.55 and 0.17 for SLOdm and GMT ratio of 39.14 and 0.13 for BP-2a	Cationic nanoemulsion (CNE)-SAM expressing bacterial antigens. GAS Streptolysin-O (SLOdm) and the GBS pilus 2a backbone protein (BP-2a))	[37]

a pandemic.[79] It is clear from the immediate availability of mRNA vaccine amidst a pandemic that this technology holds promise and can be scaled up from a small batch required for the clinical trials as well as massive production in case of a global pandemic.[80]

Various mutants of SARS-CoV-2 have emerged so far. The first one to emerge was spike mutation D614G, which enhanced the spike binding to ACE2 receptor.[81] The next one to emerge was N501Y found in multiple locations on the globe including the UK (B1.1.7), Brazil (P.1) and South Africa (B.1.351). This mutant strain increases the binding of the spike to the ACE2 receptor and enhances the viral transmission.[82,83] Another mutation E484K has emerged in many variants that emerged in New York (B.1.526), Nigeria (B.1.525) and the Philippines (P3).[84,85] It has been observed that the BNT162b2 mRNA vaccine confers neutralizing activity against B.1.1.7, B.1.351, B.1.429, B.1.526, P.1 and B.1.1.7/ E484K mutant viral strains.[86] Recently, new strains B.1.617.2, B.1.617.2 and B.1.618 have spread to various countries. All these variants are currently circulating in the US. New strains included WT, B.1.525-spike, B.1.617.1-spike, B.1.617.2-spike, B.1.617.2-v2-spike, and B.1.618-spike viruses. BNT162b2 demonstrated neutralization of all the variants except for B.1.617.1, which was least neutralized, probably due to the presence of both L452R and E484Q substitutions at the receptor-binding site.[84]

Moderna has designed a new booster candidate (mRNA-1273.351) against the B.1.351 variant. mRNA-1273.351 has advanced to Phase III clinical trials in the US to assess the immunological benefit of boosting with strain-specific spike proteins.[87,88] mRNA-1273 has now been approved for a third dose booster against SARS-CoV-2 in the US (NCT04927065). Pfizer and BioNTech have also evaluated the safety and immunogenicity of a third booster dose of the BNT162b2 vaccine. This study aimed to understand the efficacy of booster dose against the South African variant. This vaccine has now been approved for the third dose booster against SARS-CoV-2[89] (NCT04955626). Initially, there were some concerns regarding the safety of mRNA-based vaccines for vulnerable groups such as the elderly, children, pregnant women, and immunocompromised patients. However, emerging data from phase II/III clinical trials show that mRNA vaccines are safe for administration in children and pregnant women[90,91] (NCT04796896, NCT04816643, NCT04958304, NCT04754594). With the success of mRNA vaccines for SARS-CoV-2, it is evident that in the future mRNA vaccine platform can be expanded to other infectious diseases.

Rabies

Rabies is a disease of the central nervous system caused by the rabies virus. Rabies virus is a member of the rhabdovirus family and bullet or rod-shaped single-stranded, negative-sense enveloped RNA virus.[92,93] The virus is transmitted from the bite of an infected mammal (cat or dog) to humans. After infection, humans develop flu-like symptoms followed by severe neurotropic symptoms caused by progressive encephalomyelitis.[16] Various vaccines have been approved against the rabies virus but still, there is high mortality due to rabies infection.[94] Thus, there is a need for better and efficacious vaccine candidates. Various mRNA-based rabies vaccines are being tested in clinical trials. CV7201 and CV7202 are two such lyophilized, temperature-stable mRNA candidate vaccines consisting of mRNA encoding the rabies virus glycoprotein (RABV-G) in free form and complexed with the cationic protein protamine.[17] CV7201 was approved for Phase 1 clinical trials in Germany. A total of 101 participants were enrolled and a total of 306 doses of mRNA were administered. Vaccination by needle-free induced virus-neutralizing antibody titers of 0.5 IU/mL in 32 (71%) of 45 participants given 80 µg or 160 µg CV7201 doses intradermally and six (46%) of 13 participants given 200 µg or 400 µg CV7201 doses intramuscularly. After a year, eight (57%) of 14 participants were boosted with an 80 µg needle-free intradermal dose of CV7201 and achieved titers of 0.5 IU/mL or more. The vaccine was ineffective in only one participant (320 µg intradermal vaccination) with a detectable immune response. CV7202 is a new vaccine for rabies virus which is still under phase 1 clinical trials.[17,95,96] So far, 53 participants have been recruited and the study is expected to be completed by 2023.

Influenza

Influenza is caused by influenza viruses, which are members of the Orthomyxoviridae family.[97] They are negative-sense single-stranded RNA viruses. Influenza virus consists of RNA polymerase subunits, viral glycoproteins (haemagglutinin (HA), neuraminidase (NA)), nucleoprotein (NP), matrix protein (M1), membrane protein (M2), nonstructural protein (NS1) and nuclear export protein (NEP).[98] In humans, influenza viruses A and B cause infectious respiratory illness.[99] Like SARS-CoV-2, severe influenza pandemic led to >40 million deaths worldwide in 1918.[100] Henceforth, there is a need for an effective influenza vaccine. Currently, three influenza vaccines are administered in the clinic: inactivated, live attenuated and recombinant HA vaccines. These vaccines target the HA protein responsible for viral entry in the host. However, the rapid mutation in the virus causes antigenic drift, which leads to yearly modification of the influenza vaccine.[101] Therefore, there is a real need for alternative antigen targets and rapid vaccine production as soon as the new influenza strain emerges. Several mRNA vaccines have been developed for influenza virus.[102] VAL-506440 vaccine consists of modified mRNAs encoding the full-length, membrane-bound form of the hemagglutinin (HA) glycoprotein from the H10N8 influenza strain or the H7N9 influenza strain in lipid nanoparticles (LNP). For both vaccines, the immunogenicity outcomes measured were HAI (humoral immunization inhibition) and MN (microneutralization assays).[31,103] A total of 201 participants were recruited for the H10N8 study. The 100-µg intramuscular dose induced HAI titers $\geq$1:40 in 100% and MN titers $\geq$1:20 in 87.0% of the participants. The 25-µg intradermal dose induced HAI titers >1:40 in 64.7% of the participants compared to 34.5% of the participants receiving the IM dose.[104]

For H7N9, 156 participants were chosen, intramuscular doses of 10, 25, and 50 µg achieved HAI titers $\geq$1:40 in

36.0%, 96.3%, and 89.7% of the participants, respectively. MN titers ≥1:20 were achieved by 100% in the 10- and 25-μg groups and 96.6% in the 50-μg group. Seroconversion rates identified were 78.3% (HAI) and 87.0% (MN) for H10N8 (100 μg IM) and 96.3% (HAI) and 100% (MN) in H7N9 (50 μg).[104] These high neutralization antibody titer data from clinical trials suggest that mRNA vaccines hold a great promise against influenza infection.

Respiratory Syncytial Virus (RSV)

RSV is caused by a negative-sense, single-stranded RNA virus that belongs to the Paramyxoviridiae family.[105] RSV consists of M2-1 (transcription processivity factor), M2-2 (switches transcription to DNA replication. It also consists of lipid bilayer displaying the fusion (F), attachment (G), and small hydrophobic proteins (SH).[106] RSV infection leads to acute bronchiolitis in children and is associated with high morbidity and mortality. Current RSV vaccine candidates target the highly conserved F protein, which prevents viral fusion; however, most of them failed the clinical trials because of insufficient neutralizing antibody titers. Recently, mRNA-1345 has been developed as the potential mRNA-based vaccine for RSV.[107] The sequence of mRNA-1345 has been engineered and codon-optimized to enhance translation and immunogenicity relative to the previous vaccine candidate mRNA-1777.[108] The mRNA encodes for a stabilized prefusion F glycoprotein of RSV by engineering the coding sequence. The Phase I clinical trials for mRNA-1345 are still ongoing. A total of 160 participants have been recruited so far, and tolerability and reactogenicity of several doses of mRNA lipid nanoparticle injections on adults and children will be evaluated by the completion of the study in 2023.[108]

Human Metapneumovirus (HMPV) and Parainfluenza Virus Type 3 (PIV3)

Human metapneumovirus and parainfluenza virus are respiratory pathogens that belong to the Paramyxoviridiae family. HMPV is a negative-strand RNA virus that encodes three viral glycoproteins: fusion (F), attachment (G) and short hydrophobic proteins (SH). HMPV causes respiratory tract infections in infants and young children.[109] PIV3 is a single-stranded negative-sense RNA virus. It consists of three nucleocapsid associated proteins, the nucleoprotein (N), phosphoprotein (P), large polymerase protein (L), an accessory protein (C) encoded by the second open reading frame (ORF) in the P mRNA; an internal matrix protein (M) and two envelope-associated proteins, the fusion (F) and the hemagglutinin-neuraminidase (HN) glycoproteins, which are the major neutralization and protective antigens.[110] Currently, there is no licensed vaccine for HMPV and PIV3; however, several vaccine candidates have been developed which are being tested in preclinical studies. An mRNA vaccine, mRNA-1653 targeting fusion proteins (F protein) of both HMPV and PIV3 has been evaluated in phase I clinical trials. A total of 160 patients were recruited to evaluate the safety, reactogenicity and immunogenicity of the vaccine in children and adults. The interim results indicate that 1 month after a single vaccination, geometric mean titers were 6.04 for HMPV-A, 6.33 for HMPV-B and 3.24 for PIV3. Second interim data demonstrated that the antibody titers remained above the baseline after 7 months post vaccination[111] (NCT04144348). Therefore, mRNA vaccines have the potential to prevent significant virus-associated morbidities and mortalities worldwide due to HMPV and PIV3.

Human Cytomegalovirus (HCMV)

Human cytomegalovirus belongs to the human herpes type 5 family. These viruses have a double-stranded linear DNA in an icosahedral nucleocapsid with a protein matrix.[112] HCMV can be transmitted via direct transmission from human to human.[113] There are numerous candidate vaccines against HCMV infection and disease in development. However, no vaccine has been approved for administration.[114,115] mRNA vaccine candidates, mRNA-1647 and mRNA-1443 use envelope glycoprotein B precursor (gB) to generate neutralizing antibodies against HCMV. These mRNA vaccines were tested for their safety, reactogenicity and tolerability in phase I clinical trials. For mRNA-1647, CMV-seropositive groups who received 30 μg, 90 μg and 180 μg groups had geometric mean ratios (GMRs) of the neutralizing antibody ranging from 14-fold to 31-fold across the three doses against epithelial cell infection whereas the GMRs against fibroblast infections were 6-fold to 8-fold. For Phase II, CMV-seropositive groups who received 50 μg, 100 μg and 150 μg groups had geometric mean ratios (GMRs) of the neutralizing antibody ranging from 12-fold to 14-fold across the three doses against epithelial cell infection, whereas the GMRs against fibroblast infections were 0.8-fold to 1.2-fold (NCT03382405). These high neutralizing antibody titers suggest that mRNA

vaccines against HCMV infections may offer protection against this lethal disease.

Zika Virus

Zika is caused by the Zika virus (ZIKV) which is an arthropod-borne virus that belongs to the Flaviviridae family. Zika virus is transmitted to humans by the bite of Aedes mosquitoes and then direct transmission from human to human via saliva or sexual contact from an infected person. Zika is a positive-sense RNA virus consisting of three structural proteins: capsid (C), pre-membrane (prM), envelope (E) and seven structural proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B and NS5). ZIKV infection leads to mild influenza-like illness and multi-organ failure, meningitis, and encephalitis in severe cases.[116] The common antigen choice for mRNA vaccines against Zika virus is the membrane and envelope protein (prM-E) as the neutralizing antibodies against prM-E can prevent viral fusion. One study showed that a single 30 µg or 50 µg dose of an LNP-prM-E mRNA-protected mice and rhesus macaques, respectively, from a Zika infection. The neutralizing antibody titers generated by the mRNA vaccine were 50–100 times higher than other vaccines.[117,118] mRNA-1893 is another mRNA-based vaccine that targets pre-membrane and envelope (prM-E) glycoproteins of the Zika virus. prM-E is an antigen choice for mRNA vaccines against Zika virus because the neutralizing antibodies against it prevent viral fusion to the host cell. Phase I clinical trials of this vaccine to evaluate the safety, tolerability and immunogenicity are underway and expected to be completed by 2021 (NCT04917861). mRNA1325 is another mRNA-based vaccine that completed the phase I clinical trials in 2019 but the data has not been published yet (NCT03014089). So far there is no approved vaccine against the Zika virus, hence these mRNA-based vaccines are of therapeutic value against Zika virus infection.[119]

Epstein–Barr Virus (EBV)

Epstein–Barr virus, the causative agent for mononucleosis belongs to the Herpes family. EBV consists of a torsoid-shaped protein core, envelope protein, double-stranded DNA, icosahedral capsid of 162 capsomeres, a viral tegument and nucleocapsid. EBV is transmitted via direct transmission from saliva of infected individuals. Efforts have been made to develop a prophylactic vaccine against EBV to prevent primary infection and subsequent chronic disease but there is still no vaccine for clinical use.[120] mRNA-1189 is an RNA vaccine against antigen glycoprotein 350 (gp350).[121] Only preclinical studies have been conducted so far. Naïve Balb/c mice were administered with two doses of mRNA-1189 and the antibody titers against viral proteins involved in epithelial cell entry (gH/gL and gB) or B cell entry (gp350, gH/gL and gB) were measured in peripheral blood after 57 days (ModernaTx). With the development of these two mRNA vaccine candidates and improvements in antigen selection, there is hope for sustainable immunity and protection against EBV-associated malignancies.

Human Immunodeficiency Virus (HIV)

HIV causes acquired immunodeficiency syndrome (AIDS) and belongs to the Retroviridiae family.[122] Structurally, HIV is composed of a 5′ long terminal repeat region (LTR) which codes for promoter for the transcription of viral genes, the reading frame of *gag* gene encoding outer core membrane (MA), capsid protein (CA), the nucleocapsid (NC) and a nucleic acid stabilizing protein. After *gag, pol* gene encodes for protease (PR), reverse transcriptase (RT), RNase H and integrase (IN). Adjacent to *pol* gene, *env* gene encodes two envelope glycoproteins gp120 and gp41.[123] HIV emerged as a pandemic and globally 17.5 million people were infected by the virus. HIV is transmitted via direct human to human transmission.[123] Despite numerous years of research, there is still no effective vaccine against HIV due to the antigenic diversity of the envelope protein and the dense "glycan shield" that conceals the envelope protein epitopes. There have been efforts to develop mRNA vaccines against HIV in recent years.[124] Self-amplifying mRNA vaccine encoding a clade C envelope glycoprotein and viral replicon particle (VRP) was evaluated in rhesus macaques. Animals receiving the HIV SAM and HIV-VRP vaccines reached anti-Env levels of 10^3–$10^{4.5}$, with GMTs of $10^{3.94}$ and $10^{3.41}$, respectively.[24,124] Anti-Env antibody titers increased significantly after boosting with Env/MF59, reaching levels 10–100-fold higher than those found after priming with peak GMTs of $10^{6.14}$, $10^{6.25}$, and $10^{4.79}$ for Env/MF59, HIV SAM, and HIV-VRP respectively.[125,126] Another preclinical study investigated the mRNA encoding *gag* gene of HIV which induced antigen-specific, functional T cells resulting in potent cytotoxic T lymphocytes.[28] One study investigated the effect of intravenous injection of an LNP-encapsulated, nucleoside-modified mRNA expressing

VRC01, to produce neutralizing antibodies in mice. This approach using a single dose protected mice from intravenous challenge with HIV-1.[127] Hence mRNA vaccines have the potential to become efficacious vaccine candidates against HIV infection.

Streptococcus

Streptococci are coccoid gram-positive bacteria. They are non-motile and form spores. They cause numerous diseases and invasive infections. There are three groups of *Streptococcus*: Group A, B and C. Invasive Group A *Streptococcus* (GAS) causes infection of the skin, soft tissue, and respiratory tract. Most of the GAS infections are severe and, in some cases, fatal. Group B *Streptococcus* (GBS) leads to invasive infections in infants, pregnant women, and older adults. GBS infection leads to pneumonia, meningitis, and sepsis. Group C *Streptococcus* infection is zoonotic and transmitted from exposure to infected farm animals. Group C infection leads to infections in the skin and soft tissues. Currently, there are no vaccines approved against GAS/GBS and due to severity of the infections, there is an urgent need for a vaccine.[128] Recently, self-amplifying mRNA (SAM) has been used to develop vaccines against GAS and GBS. Bacterial antigens (the double-mutated GAS Streptolysin-O (SLOdm) and the GBS pilus 2a backbone protein (BP-2a)) were expressed by SAM vectors. These SAM vectors bound to cationic nano-emulsion (CNE) were tested for immunogenicity in CD-1 mice. For immunogenicity, GMT of BP-2a after 2 and 3 weeks were 4.7×10^2 and 4.7×10^3, respectively. GMTs of SLOdm after 2 and 3 weeks were 1.25×10^4 and 2.5×10^4, respectively.[37]

Ebola Virus

Ebola virus belongs to the Filoviridae family. Ebola virus is composed of negative-sense RNA, surface glycoprotein, lipid membrane envelope and tubular helical nucleocapsid. Ebola virus is a zoonotic virus transmitted from vertebrate animals to humans and other mammalian species.[129] The secondary transmission occurs from human to human by contact with infected blood and body fluids. The virus affects the gastrointestinal system and the central nervous system. In severe cases, it leads to multi-organ failure, coma, and death. Ebola emerged as an endemic in Central Africa in 2014.[130] Although the FDA approved a recombinant vesicular stomatitis virus (VSV)-based Ebola vaccine (rVSV-EBOV) in 2019, there are some safety concerns including acute arthritis and skin rash at high doses.[131] mRNA vaccines against the Ebola virus may prove to be safer than this virus-based vaccine as they do not replicate inside the body. Two mRNA vaccines based on the EBOV envelope glycoprotein (EBOV GP) were developed. The mRNAs were encapsulated with lipid nanoparticles to facilitate delivery. The vaccine was tested for neutralizing antibodies in guinea pigs. Two groups (vaccine A, B) of guinea pigs were immunized with the two vaccines. EBOV GP serum IgG was detected in both groups after 21 days. After 42 days, EBOV GP titers were increased in the Vaccine B group. After the second dose, the vaccine A group has 1:140, while vaccine B group increased to 1:1800.[132]

Advantages and Challenges Associated with mRNA Vaccines

mRNA vaccines are advantageous because mRNA is non-infectious and does not integrate into the genome. In addition, the incorporation of modified nucleosides in the mRNA sequence reduces its inflammatory capacity. Hence, mRNA-based vaccines are safer than other virus-based vaccines.[10] mRNA-based vaccines have several benefits over conventional vaccines, in that they are precise and only express a specific antigen and induce a directed immune response. These vaccines promote both humoral and cellular immune responses and induce the innate immune system. mRNA expression in the body does not require nuclear entry, which diminishes the possibility of genomic integration.[36] mRNA is quickly degraded by cellular processes after the induction of immune response. The mRNA vaccine manufacturing is easily standardized because a change in the antigen does not affect the mRNA backbone's physical-chemical characteristics. Additionally, the safety concerns for the viral contaminants are minimized since production is based on an in vitro cell-free transcription reaction.[133] Although there are several benefits of mRNA vaccines, certain challenges also exist. Currently, a well-established manufacturing platform for the generation of mRNA is lacking and several combinations of manufacturing steps are required. These can be grouped into upstream processing, which comprises the enzymatic generation of mRNA, and downstream processing, which includes the unit operations required to purify the mRNA product.[8] In addition, the need for cold chain storage for mRNA vaccines poses logical difficulties. Therefore, there is a need for the

development of thermostable vaccines for warm countries or those without reliable cold chain storage.

Concluding Remarks

Although mRNA vaccines have been in existence for almost three decades, these vaccines were approved for emergency patient use for the SARS-CoV-2 pandemic by the FDA. There is a need for understanding the molecular mechanism of action of mRNA vaccines.[134] Continual optimization of UTRs and coding mRNA will provide greater stability and potency of the vaccine in terms of the production of antigens in the body. In addition, improved stability of mRNA vaccines can also be achieved using base or sugar modifications that can lead to higher translational properties. The optimization of carrier systems such as the development of ionizable lipids and formulations, enhanced cellular uptake, endosomal release, and enhanced potency is desired.[135] Bioinformatics tools can be utilized for sequence optimization of coding mRNA sequences. These tools can also assist in predicting the correlation between preclinical and clinical studies on mRNA vaccines.[136] The focus of current mRNA vaccines is to optimize immunogenicity and efficacy while monitoring the safety of the vaccine in humans. Activation of immune response can be advantageous but can also lead to some complications. Hence, there is a need to optimize the titers of the vaccine dose, therefore there is a need for the design of clinical trials in a way that captures the immune response effectively.[8,52,137] Several technologies such as transcriptomics and proteomics-based approaches can be used to identify these immune responses.[138] The humoral response generated by the mRNA vaccines so far has not been at par as compared to the live attenuated vaccines. Therefore, a detailed investigation is required to identify formulations that will enable achieving the desired immune responses.[8,139] Currently, the regulatory guidelines on the clinical development of mRNA vaccines have not been fully outlined. There is a need to develop guidelines for the study of novel carriers of mRNA vaccines and monitor their safety and efficacy.[70]

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

All authors affiliated with Fosun Pharma USA Inc., and Shanghai Fosun Pharmaceutical Industrial Development, Co., Ltd. The authors report no other conflicts of interest in this work.

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